REMARKS

Applicants have canceled claims 18-24 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended claim 1 and added new claim 25-39. Support for these amendments can be found throughout the specification as filed, for example, at Example 17. Accordingly, no new matter is introduced by these amendments.

35 U.S.C. § 103(a) – Obviousness

Claims 1-3 and 7-24 are rejected under 35 U.S.C. § 103(a) as obvious over Bennett (US 6,096,722) in view of Knobler (1986), Madden (1990), Subramani (1993) and Patel (1995). The Examiner asserts that the '722 patent discloses the use of ISIS 2302 as an enema formulation and for treatment of Crohn's disease (CD), ulcerative colitis (UC), inflammatory bowel disease and regional enteritis. The Examiner cites several other references to support the assertion that pouchitis resembles UC and that patients with pouchitis have elevated levels of plasma ICAM-1. Based on the above, the Examiner asserts that it would be obvious to use an enema formulation of ISIS 2302 to treat pouchitis with a reasonable expectation of success.

The Examiner also rejects claims 1-3 and 7-24 under 35 U.S.C. § 103(a) as obvious over Gewirtz (2001) in view of Madden (1990), Subramani (1993) and Patel (1995). The Examiner asserts that Gewirtz reports the history of the clinical development of ISIS 2302, including administration as an enema. While Gewirtz does not teach the treatment of pouchitis, the Examiner relies on the other references for the assertion that pouchitis is similar to UC, CD and IBD. The Examiner asserts that it would be obvious to use an enema formulation of ISIS 2302 to treat pouchitis with a reasonable expectation of success. Applicants respectfully traverse.

Without acquiescing to the Examiner's rejections, and solely in the interest of advancing prosecution, independent claim 1 recites specific endpoints required by the recited methods. Specifically, claim 1 requires that the treated human be suffering from "chronic, unremitting pouchitis," and that the treatment "reduces the occurrence of one or more clinical symptoms selected from the group consisting of stool frequency, rectal bleeding, fecal urgency, abdominal

cramps, and fever, and wherein said treatment reduces said PDAI score to less than 7." These endpoints are found in the results of Example 17 of the instant specification. None of the cited references teach that the treatment of a human with chronic, unremitting pouchitis with the claimed methods can result in a reduction of PDAI score to less than 7.

The Examiner states that the '722 patent discloses "that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55," and that "the therapeutic efficacy of ISIS 2302 in an enema formulation for treatment of inflammatory bowel disease, Crohn's disease, and UC was known in the art as clearly taught and claimed in the ['722 patent]." *Office Action* at 4 and 6. The Examiner also asserts that "alicaforsen enema was known to have a therapeutic potential to treat a wide range of inflammatory disorders, including inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) as taught by Gewirtz et al." *Id.* at 9.

Applicants note that the cited portion of the '722 patent, Examples 51-55, report that clinical trials on ISIS 2302 are underway, but there are no results reported for Examples 51, 53, 54, and 55. While there are results reported for Example 52, where ISIS 2302 shows promising results for the treatment of Crohn's disease, the compound was administered intravenously, not by enema. Thus, contrary to the Examiner's assertion, the '722 patent does not report any results on the use of ISIS 2302 as an enema for the treatment of any human disease.

In addition, the Examiner is ignoring the teachings of Gewirtz reference cited by the Examiner. As the Examiner notes, Gewirtz reports on the clinical studies of ISIS 2302 (alicaforsen). While Gewirtz does teach that alicaforsen has therapeutic potential, it is the authors' opinion that that potential has not yet been realized. Under the heading of "Current Opinion," the authors state that "[w]hether alicaforsen can reduce ICAM-1 expression in humans to an extent significant enough to be therapeutic in [Crohn's disease], at drug concentrations that do not cause unacceptable side effects, has yet to be determined." *Gewirtz* at 1403, col. 2, first paragraph (emphasis added). In addition, Gewirtz states that "[w]hile the overall available data suggest the drug has some therapeutic benefit toward this disorder [CD], additional clinical trials are necessary before any reasonable assessment of its value can be made." *Id.* at col. 2, second paragraph (emphasis added).

Based on the above, it is clear that none of the cited references provide a reasonable basis for one of skill in the art to expect the benefits reported in Example 17 of the instant specification in the treatment of pouchitis, for example that 58% of patients would be in remission following treatment. The '722 patent does not report the successful treatment of any human disease using an enema formulation of ISIS 2302, and does not even mention pouchitis. The Gewirtz reference states that it remains to be determined if ISIS 2302 can be successfully used to treat CD, and likewise does not mention the treatment of pouchitis. Thus, the results in Example 17 are unexpected, and the pending claims are not obvious over the cited references. Applicants therefore request reconsideration of the rejection of the claims under 35 U.S.C. § 103(a) over the cited references.

Double Patenting Rejection over U.S. Patent 6,169,079

Claims 1-3 and 7-24 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 6,169,079 in view of Patel. The Examiner argues that it would have been obvious to select ISIS 1939 or ISIS 2302 from the antisense compounds disclosed in the specification of the '079 patent because "either compound was the identified, predictable solution among the finite number of identified, predictable options within the technical grasp of one of ordinary skill in the art." *Office Action* at 14. The Examiner asserts that the specification of the '079 patent also teaches rectal administration in the form of suppositories. Finally, the Examiner relies on Patel for the disclosure that patients with pouchitis have elevated ICAM-1. The Examiner concludes that since ISIS 1939 and 2302 target ICAM-1, "it would have flowed logically to one of ordinary skill in the art at the time the invention was made to apply the method of claim 3 of [the '079 patent] to treat pouchitis in a human by formulating ISIS 2302 for rectal use. Applicants respectfully traverse.

As explained above in responding to the 35 U.S.C. § 103(a) rejection of the claims over the '722 and Gewirtz references, Example 17 of the instant specification reports unexpectedly good results in the treatment of pouchitis using the claimed methods. According to the Examiner, the specification of the '079 patent "does not contain any *in vivo* working examples for any ICAM-1 antisense oligonucleotides targeted to 'human' sequence," and the cited claim "does not recite treatment of pouchitis *per se*." *Office Action* at 12 and 14. When combined with

the teachings of Gewirtz, which call into question the therapeutic benefit of ISIS 2302, claim 3 of the '079 patent and Patel do not provide any basis for predicting the surprising and unexpected results reported in Example 17 – e.g., 58% remission of chronic, unremitting pouchitis. Thus, for at least this reason, the pending claims are not obvious over claim 3 of the '079 patent.

In addition, as Applicants have noted in previous responses, the M.P.E.P. and caselaw are unambiguous in stating that the specification of a cited patent may not be considered in making an obviousness-type double-patenting rejection:

> When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure. *M.P.E.P. §804 II.B.1* (emphasis added).

According to the M.P.E.P., the disclosure of a patent cited for obviousness-type double-patenting can be considered for only two limited reasons. The first is to learn the meaning of a term in the patent claim, in which case the specification is used as a dictionary. *See Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). The second is to determine what is claimed by looking to an embodiment of the invention disclosed in the specification. This is done to assist the Examiner in determining what is claimed. *See In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970).

Neither of these exceptions apply to the instant case. The Examiner attempts to use the above exception to argue that one of skill in the art, reading the specification of the '079 patent, would find only two antisense disclosed in the '079 that "have therapeutic potentials via both inhibitory screening tests and *in vitro* experimental data," and that "either ISIS 1939 or ISIS 2302 would be the antisense oligonucleotide encompassed by the therapeutic method of the reference claim," and therefore one of skill in the art would have selected one of the two. *Office Action* at 13.

This is impermissible use of the specification. Once the claim scope of the '079 patent is determined by reference to the specification, it is the claim that is used to make the obviousness analysis, not the specification. Regardless of the correctness of the Examiner's statement that ISIS 1939 and 2302 are encompassed by claim 3, it is clear that claim 3 is not limited to ISIS 1939 and 2302. Because the scope of claim 3 of the '079 patent is not limited to ISIS 1939 and

2302, and these sequences are not recited in claim 3, one of skill in the art will only be led to ISIS 2302 by impermissibly relying on the specification to make their selection. The Examiner is impermissibly relying on the teachings of the '079 patent to select the species of ISIS 2302 from all of the species of antisense molecules that fall within the scope of claim 3 of the '079 patent when ISIS 2302 is not disclosed in claim 3 of the '079 patent. According to the M.P.E.P., this is impermissible, as the claims of the instant application must be obvious over the claim of the '079 patent, not the entire disclosure of the '079 patent.

Applicants also note that the Examiner relies on the specification of the '079 patent for the teaching that pharmaceutical compositions can be administered in a number of ways, including rectal suppositories. *Office Action* at 14. This too is an impermissible use of the specification, as the Examiner is not limiting her use of the specification to determining claim scope, but rather for specific teachings of the specification.

Applicants clarify for the record that in any past or present responses or proceedings arguing that the M.P.E.P. and caselaw state that the "the disclosure of the patent may not be used as prior art," Applicants are not asserting that a particular cited patent is not available as prior art under any statute. Rather, Applicants are arguing that when cited as a double-patenting reference, the M.P.E.P. and cases cited therein state that the disclosure of the cited patent cannot be considered in making the double-patenting rejection, except for the limited reasons discussed above.

In sum, the Examiner's obviousness-type double-patenting rejection fails because the claimed methods provide unexpectedly good results in treating pouchitis, and because the M.P.E.P. states that the Examiner may not rely on the disclosure of the '079 patent to provide a basis to select the species of ISIS 2302. Therefore, Applicants respectfully request that the obviousness-type double-patenting rejection of claims 1-3 and 7-24 over U.S. Patent No. 6,169,079 be withdrawn.

Double Patenting Rejections over U.S. Patent 6,096,722

The Examiner also rejects claims 1-3 and 7-24 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 9-11, and 16-19 of U.S. Patent No. 6,096,722 in view of Patel. To support the rejection, the Examiner argues that the

cited claims are directed to methods of treating disease including CD and UC, and that claim 16 expressly recites SEQ ID NO: 1 of the instant claims. The Examiner relies on Patel for the teaching that pouchitis results in high levels of ICAM-1. The Examiner impermissibly relies on the specification of the '722 patent for the teaching that pharmaceutical compositions can be administered in a number of ways, including rectal suppositories. *Office Action* at 15. Applicants respectfully traverse.

As noted above in the response to the 35 U.S.C. § 103(a) rejection of the pending claims over the '722 patent and Patel, the presently claimed methods have surprisingly good results in treating pouchitis as reported in Example 17. For the reasons discussed above, these results are unexpected in view of the '722 patent and the Gewirtz reference. For at least this reason, the pending claims are not obvious in view of the claims of the '722 patent. Applicants therefore respectfully request the withdrawal of the obviousness-type double-patenting rejection of the pending claims over U.S. Patent No. 6,096,722.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Examiner's attention to the following patents and/or applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
10/793,497	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	03.04.2004
6,747,014	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	06.08.2004
09/315,298	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.20.1999
11/237,063	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	09.28.2005
6,169,079	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	01.02.2001
6,300,491	OLIGONUCLEOTIDE INHIBITION OF CELL ADHESION	10.09.2001
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
6,093,811	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	07.25.2000
6,015,894	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.18.2000
5,843,738	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	12.01.1998
6,096,722	ANTISENSE MODULATION OF CELL ADHESION MOLECULE EXPRESSION AND TREATMENT OF CELL ADHESION MOLECULE-ASSOCIATED DISEASES	08.01.2000
6,111,094	ENHANCED ANTISENSE MODULATION OF ICAM-1	08.29.2000
10/454,663	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	06.04.2003
6,849,612	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	02.01.2005
6,887,906	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	05.03.2005
08/886,829	COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL	07.01.1997

07/939,855	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.02.1992
5,591,623	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	01.07.1997
5,514,788	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	05.07.1996
5,883,082	COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING ALLOGRAFT REJECTION	03.16.1999
07/567,286	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	08.14.1990
10/559,401	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	N/A
09/659,288	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION	09.12.2000
09/082,624	COMPOSITIONS AND METHODS FOR NON-PARENTAL DELIVERY OF OLIGONUCLEOTIDES	05.21.1998

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/22/08

By: _____

Brenden S. Gingrich
Registration No. 60,295
Attorney of Record
Customer No. 55,389
(619) 235-8550

5909530
091008